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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,894	12/15/1999	MARC PIECHACZYK	19141-007	5731

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EXAMINER	
SGAGIAS, MAGDALENE K	
ART UNIT	**PAPER NUMBER**
1632	

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10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/341,894	PIECHACZYK ET AL.	
	Examiner	Art Unit	
	Magdalene K. Sgagias	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52,53,55,60 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-53, 55 and 60-61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/7/07 has been entered.

Claims 52-53, 55 and 60-61 are pending and under consideration. Claims 1-51, 54, and 56-59 are canceled.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 52-53, 55 and 60-61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of delivering an antibody or a fragment thereof to a subject mammal without triggering an anti-idiotype response directed against said antibody in said mammal, said method comprising transplanting a genetically modified mammal cell which comprises a polynucleotide comprising:

(i) a nucleotide sequence encoding an antibody or fragment thereof to be delivered;

(ii) a promoter sequence controlling expression of the nucleotide sequence from (i) in the cell

and (iii) an element guaranteeing the secretion of the encoded antibody or fragment thereof; wherein said polynucleotide is expressed and the cell secretes the encoded antibody or fragment thereof such that the antibody or fragment thereof reaches the blood circulation of the subject mammal; wherein said cell is a cell not specialized for the production of antibodies, which has the ability (a) to secrete proteins, (b) to live in the mammal subject, and wherein said cell derives from the subject mammal or from another mammal, which is a compatible donor and wherein an anti-idiotypic response is not triggered.

The specification teaches that C2C12 cells genetically modified with mouse anti-human thyroglobulin monoclonal antibody (Tg10) and which retained the capacity to differentiate into myotubes **in vitro** were implanted via injection in the forelegs of syngenic C3H mice and the production of recombinant antibodies having retained the thermodynamic properties, and the recognition property of the initial antibody antigen was followed for two months (specification example 6). The specification teaches the quantity of antibody produced was regularly elevated from the base level to a production of approximately 100 ng/ml of serum (specification, example 6). The specification also contemplates that one of the essential goals of the invention is to systemically produce a recombinant antibody, beneficially therapeutic by genetically modified mammalian cells [0091-0091]. The specification teaches that a possible risk of this approach is the induction of an immune response on the part of the modified organism capable of neutralizing the recombinant antibody [0095]. The specification also discusses that this potential problem was avoided in the experimental results presented in their example 6 primary myogenic cells expressing a stable Tg10 monoclonal antibody after retroviral transduction were implanted at the level of the tibialis anterior of the C3H mouse [0096] and the quantity of Tg10 antibody secreted was dosed with the ELISA method and in parallel, the quantity of anti-idiotype antibody was determined by ELISA [0093-0096]. The specification discusses that no anti-

idiotype response could be detected under these conditions [0097]. While the specification teaches that in said mice the quantity of the antibody was monitored by ELISA and no anti-idiotypic response could be detected under these conditions, however, the specification fails to provide guidance to correlate the levels of the Tg10 antibody produced to the lack of an induced anti-idiotypic response and moreover, wherein said transduced cell is capable of differentiating into a tissue but retains the ability to secrete the antibody, and furthermore wherein said secreted antibody in the blood is a therapeutic antibody at therapeutic levels. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating any the diseases disclosed in the specification by way of the claimed method. It would have required undue experimentation to make and use the claimed invention without a reasonable expectation of success.

At the time of the instant invention the art of transplantation of ex vivo genetically engineered cells, for the production of antibodies by a genetically engineered ectopic cell (that is a cell other than a B cell) comprising a transgene encoding for an antibody and then transplanting said cell in a mammal, resulting in the expression and secretion of the antibody in vivo, wherein an anti-idiotypic response is not triggered was unpredictable without undue experimentation. With regard to cell-based gene therapy in vivo, while progress has been made in recent years, cell transfer, homing and expression of a transgene at therapeutic levels without triggering an anti-idiotypic response to the transgene continuous to be a difficulty s supported by teachings in the art. The art of allogeneic or xenogeneic cell antibody-mediated gene/cell therapy is an unpredictable art with respect to the survival of non-antibody producing cells (that is ectopic antibody producing ***cells***) in vivo, levels of recombinant antibody produced after transplantation, in vivo. **Qu et al,** (The Journal of Cell Biology, 142: 1257-1267, 1998) at the time of the instant invention reports the application of cell and gene therapy in combination is

facing major hurdles (p 1258, 2nd column, last paragraph). Qu reports through the combination of myoblast transplantation and gene therapy, the ex vivo gene transfer approach has been investigated as a gene delivery approach in the skeletal muscle and both the ex vivo procedure and the myoblast transfer approach are limited by the poor survival of the injected myoblasts (p 1258, 2nd column). Qu also reports the origin of the myogenic cells may influence their survival (abstract).

The specification teaches the transplantation of C2C12 cells genetically modified with mouse anti-human thyroglobulin monoclonal antibody (Tg10) into syngeneic mice. **Hortelano et al,** (Haemophilia, 7: 207-214, 2001) notes that microcapsules enclosing recombinant C2C12 myoblasts genetically engineered with the transgene for secreting human factor IX after transplantation into mice even though said cells delivered the transgene into the plasma of mice as determined by ELISA, however tumors rended to appear after 6 weeks and Hertelano notes that this cell line is notorious for inducing tumorogenicity and probably the antibody levels detected before the onset of tumors at week 4 were not secreted by the tumors (p 212, under discussion). A such it is not clear the Tg10 antibody detected after two months of the transduced C2C12 myoblasts in the instant invention is secreted by tumorigenic C2C12 cells.

Bendandi (Leukemia, 14: 1333-13339, 2000) notes that idiotypes are located in the hypervariable regions of the immunoglobulin (Ig) variable domain, and are recognized as being foreign due to the fact that the tiny quantity present in any individual is insufficient to induce self tolerance (p 1333, 1st column, 2nd paragraph). Furthermore, the differences between donor and recipient idiotypes may be functionally relevant in the context of B cell function regulation (Bendandi et al, p 1333, 1st column, 2nd paragraph). The disclosed example 6 in the specification provides general guidance for producing an antibody in a subject, however fails to address any issue regarding any immune response(s) and antibody production in said subject to

the production of a foreign antigen, in this case a recombinant antibody, wherein an anti-idiotypic response is not triggered against the recombinant antigen. Therefore, the skilled artisan would conclude that the state of art of transplantation of genetically engineered cells with a gene encoding an antibody in vivo, wherein an anti-idiotypic response is not triggered is undeveloped and unpredictable at best. Given the lack of guidance provided by the instant specification, it would have required undue experimentation to practice the invention as claimed for treating any of the disclosed diseases by way of the claimed method without a reasonable expectation of success.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for transplanting a genetically engineered cell ex vivo for ectopic antibody production in vivo, without triggerring an anti-idiotypic repsonse, the lack of direction or guidance provided by the specification for transplanting a genetically engineered cell ex vivo for ectopic antibody production in vivo, without triggerring an anti-idiotypic repsonse, the absence of working examples that correlate to the treatment of a disease, by way of the claimed method, the unpredictable state of the art with respect to ectopic antibody production in vivo after transplantation of a genetically engineered cell ex vivo, and in particular without triggering an anti-idiotypic response to the produced antibody, the undeveloped state of the art pertaining to the treatment of a disease by way of the claimed method, and the breadth of the claims directed to all diseases, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Magdalene K. Sgagias whose telephone number is (571) 272-3305. The

examiner can normally be reached on Monday through Friday from 9:00 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, Jr., can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Magdalene K. Sgagias, Ph.D.
Art Unit 1632

/Anne-Marie Falk/
Anne-Marie Falk, Ph.D.
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